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Methylenecyclopropanes in [4 + 1] Cycloaddition with Enones

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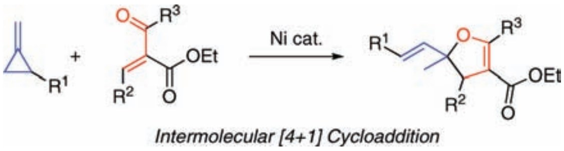
ABSTRACT



A nickel-catalyzed [4 + 1] cycloaddition of enones with methylenecyclopropanes leading to dihydrofurans was developed. The reaction outcome is attributed to the transformation of methlenecyclopropane, which is incorporated into a five-membered ring as a one-carbon fragment.

Transition-metal-catalyzed cycloaddition represents the most useful method for the synthesis of structurally diverse heterocyclic compounds from readily accessible starting materials. A formal [4 + 1] cycloaddition, in which a heterodiene and one-carbon fragment are assembled, is an attractive strategy to construct five-membered heterocyclic compounds. Therefore, development of a [4 + 1] cycloaddition of α,β-unsaturated carbonyl compounds with carbon monoxide has been a research topic of great interest.[1] In this context, it has been demonstrated that isocyanide and also a Fischer carbene complex can participate as one-carbon fragments in a [4 + 1] cycloaddition with α,β-unsaturated carbonyl compounds.[2–4]

Recently, we have developed a [4 + 2] cycloaddition of enones and alkynes to afford polysubstituted pyrans.[5] The reaction proceeds via *oxa*-nickelacycle intermediates, which are formed by oxidative cyclization of nickel(0) to enones and subsequent insertion of alkynes. We also found that the reaction of enones with allenes in the presence of a nickel catalyst affords polysubstituted dihydropyrans. In the course of our study, we next envisioned that methylenecyclopropanes (MCPs), which are classified as reactive carbon–carbon unsaturated compounds with the high ring strain energy of cyclopropane and can be as reactive as an allene, would be a good cycloaddend in the cycloaddition with enones. As a result of investigations, we found that nickel-catalyzed reactions of MCPs with enones proceed in an unexpected manner to afford [4 + 1] cycloadducts.[6] Herein, we wish to report the results: nickel-catalyzed cycloaddition of enones with MCPs incorporates MCP as a one-carbon fragment into a dihydrofuran skeleton. The utilization of MCPs as a one-carbon fragment offers an advantage in introducing quaternary carbon directly into a ring system.

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[6] For recent reviews on reactions with MCPs, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (d) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867.

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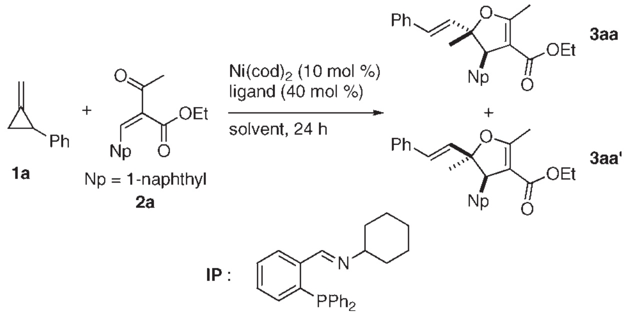
Table 1. Nickel-Catalyzed [4 + 1] Cycloaddition of **1a** with **2a**[a]



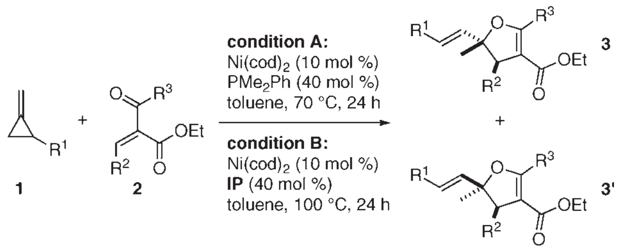
entry	ligand	solvent	temp (°C)	yield (%)[b] (**3aa**/**3aa′**)
1	$PMePh_2$	toluene	100	70 (3/1)
2	$PMePh_2$	toluene	100	58 (3/1)
3	PPh_3	toluene	100	55 (3/1)
4	PMe_3	toluene	100	66 (1/1)
5	PCy_3	toluene	100	<1 (–/–)
6	**IP**	toluene	100	77 (8/1)
7	$PMePh_2$	toluene	70	78 (11/1)
8	**IP**	toluene	70	75 (8/1)
9	$PMePh_2$	benzene	70	53 (8/1)
10	$PMePh_2$	THF	70	48 (5/1)
11	$PMePh_2$	1,4-dioxane	70	48 (2/1)
12	$PMePh_2$	MeCN	70	54 (1/1)
13	$PMePh_2$	toluene	70	5 (–/–)[c]
14	**IP**	toluene	70	<1 (–/–)[c]

[a] All reactions were carried out using **1a** (0.5 mmol, 2.5 equiv), **2a** (0.2 mmol), $Ni(cod)_2$ (10 mol %), and ligand (40 mol %) in 2 mL of solvent unless otherwise noted. [b] NMR yield is based on enone **2a**. [c] 20 mol % of ligand was employed.

Initially, it was found that the reaction of **1a** with **2a** in the presence of a Ni(0)/PMe_2Ph catalyst in toluene at 100 °C for 24 h furnished **3aa** with a 3:1 diastereomer ratio in 70% yield (Table 1, entry 1). The molecular structure of cycloadduct **3aa** was confirmed by X-ray crystal structure analysis (see Supporting Information). An investigation of a series of phosphine ligands revealed that **3aa** was obtained in lower yield with ligands such as $PMePh_2$, PPh_3, PMe_3, and PCy_3 (entries 2–5). It was found through examination of various ligands that iminophosphine **IP** is also efficient for the [4 + 1] cycloaddition[7] and **3aa** was obtained in 77% yield with a diastereomer ratio of 8:1 (entry 6). At a lower reaction temperature (70 °C), a Ni(0)/PMe_2Ph catalyst also furnished **3aa** in 78% yield with a diastereomer ratio of 11/1 (entry 7). In other solvents, such as benzene, THF, 1,4-dioxane, or MeCN, yields were even lower (entries 9–12). Decreasing the amount of ligand to 20 mol % resulted in lowering the yield of cycloadduct **3aa** (entries 13 and 14).

We next investigated the scope of the [4 + 1] cycloaddition of MCP **1** and enone **2** with respect to reaction conditions using either a PMe_2Ph ligand (condition A) or an **IP** ligand (condition B); the results are summarized in Table 2. It was found that a variety of enones **2** participate in the reaction with MCP **1b** to afford dihydrofurans **3** in good to moderate yields (entries 1–6). In general, the use of the PMe_2Ph ligand for the reaction resulted in higher yields (up to 99% yield) and also higher regioselectivity (up to **3**/**3′** = 14/1) of desired cycloadduct **3** than that of the **IP** ligand.

Table 2. [4 + 1] Cycloaddition of MCPs **1** and Enones **2**[a]



entry	R^1	R^2	R^3	**3**	condition	yield (%)[b] (**3**/**3′**)
1	Ph	Ph	Me	**3ab**	**A**	99 (12/1)
					B	77 (2/1)
2	Ph	Ph	tBu	**3ac**	**A**	<1 (–/–)[c]
					B	54 (2/1)[c]
3	Ph	Ph	Ph	**3ad**	**A**	43 (9/1)
					B	76 (1/1)
4	Ph	4-MeO-C_6H_4-	Me	**3ae**	**A**	61 (14/1)
					B	37 (2/1)
5	Ph	4-CF_3-C_6H_4-	Me	**3af**	**A**	81 (8/1)
					B	48 (2/1)
6	Ph	2-furyl	Me	**3ag**	**A**	57 (9/1)
					B	98 (2/1)
7	4-F-C_6H_4-	Ph	Me	**3bb**	**A**	85 (5/1)
					B	79 (2/1)
8	4-MeO-C_6H_4-	Ph	Me	**3cb**	**A**	83 (9/1)
					B	59 (2/1)

[a] All reactions were carried out using **1a** (0.5 mmol, 2.5 equiv), **2a** (0.2 mmol), $Ni(cod)_2$ (10 mol %), and ligand (40 mol %) in 2 mL of solvent unless otherwise noted. [b] NMR yield is based on enone **2a**. [c] 20 mol % of ligand was employed.

However, the use of the **IP** ligand is effective in the reaction of MCP **2** with enones **1** possessing a sterically hindered *tert*-butyl group or heteroaromatic group (entries 2 and 6), where the reaction with the PMe_2Ph ligand gave inferior yields. MCPs possessing electron-withdrawing and -donating aryl substituents also participated in the reaction with enone **2** to furnish dihydrofurans **3** in good yields (entries 7 and 8). The reaction of enone **2b** with alkyl substituted MCP **1d** affords **3db** along with regioisomers **3db″** (Scheme 1). We assumed that such a difference is ascribed to differences of position, where cleavage of a ring bond in cyclopropane takes place during the catalytic process.

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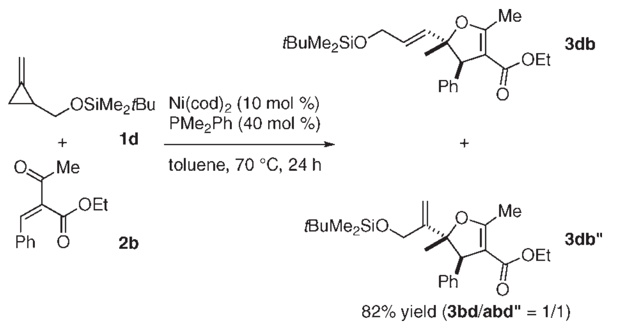
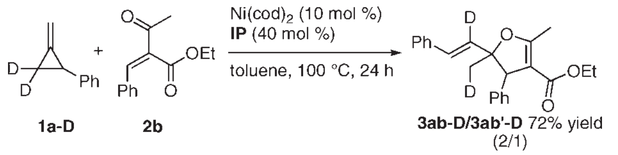
Scheme 1. [4 + 1] Cycloaddition of MCPs **1d** and Enones **2b**[a]



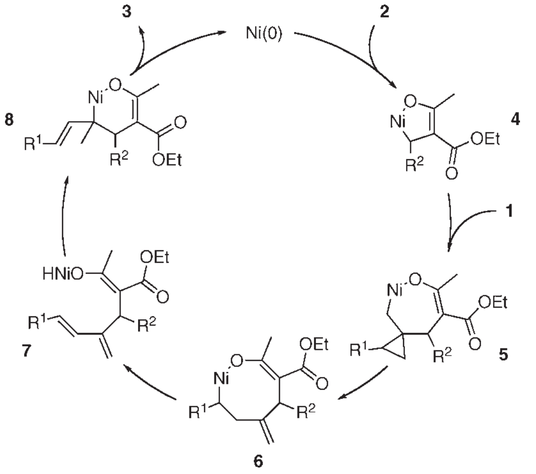
Additional experiments were performed to understand the molecular transformation of this unprecedented reaction (Scheme 2). Thus, we next examined the reaction of **2b** with deuterium labeled MCP **1a-D**; the methylene protons on this cyclopropane ring are deuterated. The reaction afforded **3ab-D** along with **3ab′-D**, suggesting that one of the methylene protons on the cyclopropane ring migrates during the transformation.

Scheme 2. Cycloaddition with Deuterium Labeled MCP **1a-D**



Based on all the data described above, we propose the following reaction mechanism, as illustrated in Scheme 3. The reaction is initiated by oxidative cyclization of enone **2** with a nickel(0) complex to furnish *oxa*-nickelacycle **4**.[8] Insertion of MCP **1** to a carbon−nickel bond of **4** is followed by ring expansion to form eight-membered *oxa*-nickelacycle **6** via cyclopropylmethyl-homoallyl metal type rearrangement.[9,10] Subsequent β-hydride elimination affords acyclic intermediate **7**; the generated hydride−nickel species of this intermediate reacts with an olefin moiety intramolecularly to furnish more thermally stable six-membered nickelacycle **8**. Reductive elimination provides **3** and regenerates the starting Ni(0) complex.

Scheme 3. Plausible Reaction Mechanism



In conclusion, a nickel-catalyzed [4 + 1] cycloaddition of methylenecyclopropanes and enones to form dihydrofurans was successfully demonstrated. In general terms, the developed reaction is an unprecedented type of cycloaddition, which incorporates an enone as a heterodiene and a methylenecyclpropane as a "one-carbon/two-electron fragment" into a five-membered ring system. This new method provides highly substituted dihydrofurans with a unique substitution pattern and thus complements the precedent [4 + 1] cycloadditions. Further efforts to expand the scope of the chemistry are currently underway in our laboratories.

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Supporting Information Available. Experimental procedures including spectroscopic and analytical data of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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